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Research report

Ventral medial prefrontal cortex inactivation impairs impulse control but does not affect delay-discounting in rats

Malte Feja*, Michael Koch

Department of Neuropharmacology, Brain Research Institute, Center for Cognitive Sciences, University of Bremen, PO Box 330440, 28359 Bremen, Germany

HIGHLIGHTS

- The $GABA_A$ agonist muscimol was used to reversibly inactivate vmPFC in rats.
- Deactivating vmPFC with low-dose muscimol induced impulsive action in the 5-CSRTT.
- High-dose muscimol infusion impaired impulse and attentional control in the 5-CSRTT.
- Muscimol into vmPFC did not affect delay-discounting in a Skinner box.
- The control function of vmPFC is impulsivity type-specific.

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ABSTRACT

Maladaptive levels of impulsivity are found in several neuropsychiatric disorders, such as ADHD, addiction, aggression and schizophrenia. Intolerance to delay-of-gratification, or delay-discounting, and deficits in impulse control are dissociable forms of impulsivity top-down controlled by the prefrontal cortex, with the ventral medial prefrontal cortex (vmPFC) suggested to be critically involved. The present study used transient inactivation of the rats' vmPFC via bilateral microinfusion of the $GABA_A$ receptor agonist muscimol (0.05, 0.5 μg/0.3 μl) to analyse its relevance for impulse control in a 5-choice serial reaction time task (5-CSRTT) and delay-discounting in a Skinner box. Intra-vmPFC injection of low-dose muscimol impaired impulse control indicated by enhanced premature responding in the 5-CSRTT, while flattening the delay-dependent shift in the preference of the large reward in the delay-discounting task. Likewise, high-dose muscimol did not affect delay-discounting, though raising the rate of omissions. On the contrary, 5-CSRTT performance was characterised by deficits in impulse and attentional control. These data support the behavioural distinction of delay-discounting and impulse control on the level of the vmPFC in rats. Reversible inactivation with muscimol revealed an obvious implication of the vmPFC in the modulation of impulse control in the 5-CSRTT. By contrast, delay-discounting processes seem to be regulated by other neuronal pathways, with the vmPFC playing, if at all, a minor role.

1. Introduction

Cognitive-executive functions, such as behavioural control and decision-making, are essential aspects of daily life in both humans and rats [1,2]. These processes are closely related to impulsive behaviour. Impulsivity is a behavioural characteristic that both adversely and beneficially affects living conditions and can function as a dimension of normal personality [3]. In case of an imbalance of behavioural activation and its inhibition, the term 'impulsivity' refers to maladaptive behaviours including inability to wait, difficulty withholding responses and insensitivity to unfavourable or delayed consequences [4,5]. High levels of impulsivity are found in psychiatric disorders, involving attention-deficit/hyperactivity disorder (ADHD), antisocial personality disorder, borderline personality disorder, schizophrenia, drug abuse and other forms of addiction [4,6,7]. Moreover, the classification of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) lists a discrete diagnostic category of 'disruptive, impulse-control, and conduct disorders' [8].

However, impulsivity is not a unitary construct, but rather a multifactorial phenomenon, largely determined by intolerance to delay-of-gratification (impulsive choice), or delay-discounting, and deficits in impulse control (impulsive action) [9,10]. Hence,

* Corresponding author. Tel.: +49 421 218 62979; fax: +49 421 218 62984.
E-mail addresses: malte.feja@gmx.de (M. Feja), michael.koch@uni-bremen.de (M. Koch).
URL: http://www.ifh.uni-bremen.de/koch (M. Koch).

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the dominant behavioural measures of impulsivity are delay-discounting and response inhibition tasks. The delay-discounting model is used in both humans and animals to assess impulsive decision-making, reflected in the preference for a small immediate over a larger-but-delayed reward [4,11–13]. By contrast, response inhibition paradigms, e. g. the 5-choice serial reaction time task (5-CSRTT), require to withhold from premature responding which is regarded as an index of deficient impulse control [14,15]. The 5-CSRTT also has translational properties and is modelled after its human analogues, the continuous performance test of attention and Leonard's five choice serial reaction time task [16].

Neuropsychological evidence suggests that executive processing relies on the intact function of the frontal cortices, with the prefrontal cortex (PFC) playing a major role [17–19]. Patients with damage to the PFC show impaired decision-making and behavioural disinhibition [17]. The human PFC is a heterogenous region of the brain, comprising the dorsolateral prefrontal cortex (DLPFC), the orbitofrontal cortex (OFC) and the anterior cingulate cortex (AC). The PFC subregions appear to be engaged in separable multi-component neural systems mediating distinct cognitive processes [20,21]. Concerning the DLPFC, inconsistent conceptions of its relevance to aspects of impulsivity exist. Decreased functioning of the DLPFC in psychopathic offenders generates impairments in impulse control [22]. However, the DLPFC is not associated with motor impulsivity measured with the Barratt Impulsivity Scale [23]. In terms of impulsive decision-making, the OFC is heavily implicated, while the DLPFC seems to play a minor role [21,24]. Yet, recent studies using repetitive transcranial magnetic stimulation link the DLPFC with delay-discounting [25,26]. AC function is related to both impulse control [27–30] and delay-discounting [31–33].

The medial prefrontal cortex (mPFC) of rats seems to combine elements of primate AC and DLPFC [34–37] and shares many features with the human medial frontal cortex [38]. Based on cellular structure and lamination of the cortex, the mPFC of rats can be further divided into dorsal (anterior cingulate and medial precentral cortices) and ventral subdivisions (infralimbic and prelimbic cortices) [39,40]. While rat dorsal mPFC is supposed to anatomically and functionally resemble primate DLPFC [35,36], the ventral medial prefrontal cortex (vmPFC) of rats appears to be equivalent to the primate AC [34]. Animal studies further strengthen the assumption of distinct aspects underlying impulsive behaviour. Findings of electrophysiological recordings [41], lesions [16,42,43] and transient inactivation [44–47] associate the rodent mPFC with impulse control. On the other hand, controversial results exist regarding the contribution of the mPFC to impulsive choice. For example, increased delay-discounting appears in mPFC-lesioned [48] or -inactivated [49] rats, whereas another delay-discounting study shows that the mPFC is not the primary site of this action [50]. There is evidence to suggest that the anatomical dichotomy of the mPFC is paralleled by functional subregional specifity, with the vmPFC appearing to be more critically involved in impulsive behaviour [42,51]. However, lesion studies revealed discrepancies in the role of the vmPFC in impulsivity, ranging from direct participation [42], a mere tendency of involvement [52] to no important role [53].

The lesion technique was the most widely used method to investigate brain function, nevertheless carrying some drawbacks in comparison to inactivation tools. Following lesions, brain tissue is destroyed irreversibly and a compensation of function by other brain areas might occur. In contrast, chemical agents like the $GABA_A$ receptor agonist muscimol allow acute, reversible inactivations of distinct brain regions, and hence, within-subject designs concomitant with increased reliability [54]. Muscimol is the psychoactive ingredient of the mushroom *Amanita muscaria* and has even a more potent pharmacological profile as the inhibitory neurotransmitter GABA itself [55]. After injection, muscimol selectively induces a rapid hyperpolarization lasting up to several hours on postsynaptic neurons via activation of $GABA_A$ receptors on the surface of local cell bodies without affecting fibers of passage [56,57].

In the present study, temporary inactivation of the rats' vmPFC via bilateral microinfusion of the $GABA_A$ receptor agonist muscimol was used to further clarify its contribution to different aspects of impulse control in the 5-CSRTT and delay-discounting in a Skinner box.

2. Material and methods

2.1. Subjects

A total of 23 adult male Lister Hooded rats (280–340 g) obtained from Harlan (Borchen, Germany) were housed in groups of four to six in standard Macrolon cages (type IV) under controlled ambient conditions (21–22 °C, 45–55% humidity, 12 h light/dark cycle, lights on at 7:00 a.m.). The animals were maintained on their experimental body weight by controlled feeding of 12 g laboratory rodent chow (Nohrlin GmbH, Bad Salzuflen, Germany) per rat per day and received tap water ad libitum. Behavioural testing took place between 8:00 a.m. and 6:00 p.m. The experiments were performed in accordance with the National Institutes of Health ethical guidelines for the care and use of laboratory animals for experiments and were approved by the local animal care committee (Senatorische Behörde, Bremen, Germany).

2.2. Experiment 1: 5-CSRTT

2.2.1. Apparatus

The 5-CSRTT was conducted in two operant aluminium chambers (26 × 26 × 26 cm; Campden Instruments Ltd., Loughborough, UK), wherein five apertures (2.5 × 2.5 cm, 4 cm deep) were inserted 2 cm above floor level in the concavely curved rear wall. This assembly provided five response options located equidistant to the food magazine on the opposite. Inside each hole, a light-emitting diode (LED) generated visual stimuli of variable duration. Nose-poke responses of the animals were detected by infra-red photo cell beams at the entrance of the apertures. The rats could be placed in the box through a Plexiglas® door on the upper part of the front wall. Underneath the door, a small Plexiglas® panel provided access to the food magazine which was lighted via two LEDs and automatically supplied with casein pellets (45 mg Dustless Precision Pellets, Bio-Serv®, UK) by an electromechanical feeder. Food collection was detected by a microswitch monitoring the movement of the hinged panel. Each chamber was illuminated by a 3 W house light mounted on the ceiling. A noise-damped fan served as ventilation and background noise of about 60 dB. The extendable grid floor facilitated the removal of excrements. For the purpose of sound attenuation, the wooden cabinet was reinforced with an insulating plate at the interior of the door. The apparatus was controlled by specific software written in Turandot (Cambridge Cognition Ltd., version 1.23) which was run on a personal computer connected to the BNC Mark 2 System (Behavioral Net Controller, Campden Instruments Ltd., Loughborough, UK).

2.2.2. Training

The animals ($n = 12$) were trained to detect the occurrence of brief light stimuli in one of the five rear wall apertures. The general procedure was based on the protocol of Campden Instruments and was divided into a habituation, pretraining and baseline training phase [58]. Before training and tests the rats were acclimatised to the laboratory for at least 30 min in their homecages.